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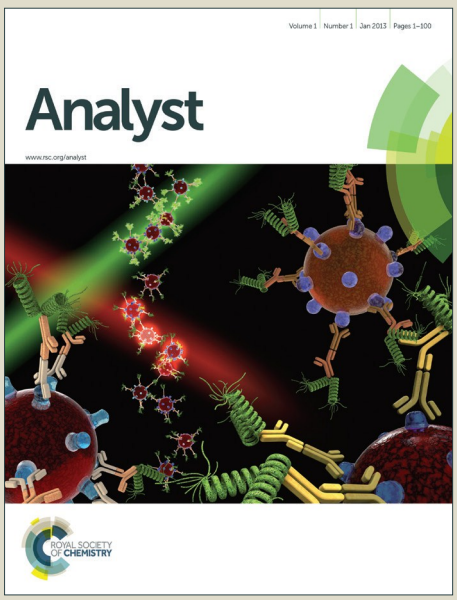

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Lab-on-Fiber Technology: A New Vision for Chemical and Biological Sensing

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The integration of microfluidics and photonic biosensors has allowed to achieve several laboratory functions in a single chip, leading to the development of the photonic lab-on-a-chip technology. Although a lot of progress has been made to implement such sensors in small and easy-to-use systems, many applications such as point-of-care diagnostic and in-vivo biosensing still require a sensor probe able to perform measurements at precise locations that are often hard to reach. The intrinsic property of optical fibers to conduct light to a remote location, makes them an ideal platform to meet this demand. The motivation to combine the good performance of photonic biosensors on chip with the unique advantages of optical fibers has thus led to the development of the so called Lab-on-Fiber technology. This emerging technology envisages the integration of functionalized materials at micro and nano scale (i.e. the labs) with optical fibers, to realize miniaturized and advanced "all-in-fiber" probes, especially useful for (but not limited to) label-free chemical and biological applications. This review presents a broad overview of the lab on fiber biosensors, with particular reference to lab-on-tip platforms, where the labs are integrated on the optical fiber facet. The light-matter interaction on the fiber tip is achieved through the integration of thin layers of nanoparticles or nanostructures supporting resonant modes, both plasmonic and photonic, highly sensitive to local modifications of the surrounding environment. According to the physical principle that is exploited, different configurations - such as localized plasmon resonaces probes, surface enhanced Raman scattering probes and photonic probes - are classified, while the various applications are presented in context throughout. For each device, the surface chemistry, and the related functionalization protocols are reviewed. Moreover, the implementation strategies and fabrication processes, either based on bottom up or top-down approaches, are discussed. In conclusion we highlight some of the further development opportunities, including the Lab-in-a-needle technology, which could find a direct, disruptive impact for localized cancer treatment applications.

Introduction

Since Clark's enzymatic electrode in 1962s[1], biosensors have been proposed for a range of applications including healthcare monitoring, clinical analysis, drug development, food monitoring, homeland security and environmental monitoring, just to name a few.

In a common sense, biosensor is a device constructed to inform about a system, requiring as less human action as possible. It is formed of sample holder, a biological recognition element which must be selective, a physical transducer to generate a measurable signal proportional to the concentration of the analytes and the signal processing unit, which gives to the analysts graphical, numerical or comparative information that they shall interpret. The recognition element can be of almost any type of biological system, from antibodies, proteins and peptides to viruses, microbes, cells and tissues. The selection of the appropriate recognition element considers not only what is the information to be obtained, but also the ease of construction of the devices employing such element and, of course, their durability and cost effectiveness.

In the last years, the healthcare and pharmaceutical sectors continuously demanded more powerful analytical and diagnostic tools for the identification of diseases, the development of new medicines, and better diagnostic tests.

High-capability optical biosensing systems are emerging as a way to achieve these goals. Based on the combination of optical materials and photonic components, optical sensing offers many advantages. For instance, the technology is non-invasive, immune to electromagnetic interference, and the risk of electrical shocks or explosions is absent. A key enabler for these systems is the development of cost effective miniaturization technology, which permits the efficient integration of mechanical, fluidic, and photonic components.

In typical biosensors, detection of specific pathogens or proteins begins by immobilizing appropriate bio-receptors on the sensing areas of a chip. When analytes are introduced into

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those areas, only the target biomolecules will be bound to their corresponding biomolecular receptors. This binding process is usually monitored with commercial analytical techniques that require transduction labeling elements, such as fluorescent dyes or radioactive isotopes, to generate a physically readable signal from a recognition event. However, labeling chemistry is expensive and time-consuming. In contrast, progress in biosensing systems, in which biomolecules are unlabeled or unmodified (label-free biosensing), have shown significant results in the last decade.

The sensing transduction signals in optical label-free biosensing platforms are based on small changes in refractive index caused by the immobilization or binding reaction of biomolecules. Chip-based photonic biosensors have measured biomolecular binding interactions using well-known photonic structures providing light manipulation and control at nanoscale, such as surface plasmon resonance (SPR)[2–3], interferometers[4–7], resonators[8–9], gratings[10–11] and photonic crystals (PCs)[12–14].

Moreover the integration of microfluidics and photonic biosensors has allowed to achieve several laboratory functions in a single chip, leading to the development of the photonic lab-on-a-chip technology[15], with reduced costs, smaller required analyte volumes, compactness and increased ease of use[16].

Although photonic sensing biochips use well-established semiconductor technology, they normally need complex optical coupling systems, such as inverted taper and grating couplers, which make the devices less cost effective. Although a lot of progress has been made to implement such sensors in small and easy-to-use systems, many applications such as point-of-care diagnostic and in-vivo biosensing still require advanced platform able to provide ever increasing performances and functionality degree as well as the capability to perform in vivo measurements at precise locations that are often hard to reach.

The property of optical fibers to conduct light to a remote location, makes them an ideal platform to meet this demand. In fact optical fiber sensors exhibit unique properties such as small-size, very light weight, flexibility but also robustness, which make them an attractive alternative with respect to other sensing technologies. In contrast to a sensor built on a chip substrate, the integration of a transducer on an optical fiber with easy measurement optics could definitely allow for remote testing in difficult environments such as in the human body for in-vivo analysis.

Indeed, microscopic cross-section and ultrahigh aspect ratio, combined with its biocompatibility and mechanical robustness/flexibility, make fiber based devices unrivaled candidates for in vivo point-of-care diagnostics, by taking advantages from easy integration with medical catheters and needles. The potentiality of integrating optical fibers with medical needles will be briefly discussed in the last section of this review.

In the last years, the strong motivation to combine the undiscussed potentialities of nanophotonics and the unique advantages of optical fibers has been the key factor at the basis of a new technological vision named “Lab-on-fiber technology”.[17–21]

Lab-on-Fiber Technology

The “Lab-on-Fiber” technology is an emerging research field which basically envisages the integration of functionalized materials and devices at micro- and nano-scale (i.e. the ‘labs’) with optical fibers, aimed to develop a novel generation of advanced “all-in-fiber” miniaturized probes, exploitable in many strategic sectors ranging from optical processing to environmental monitoring, life science, safety and security.[17]

The key concept is to transform an inert optical fiber into a multifunctional sensor where ultra compact labs are developed and ‘shrinked’ into a single optical fiber, thus destructively enlarging the conventional optical fiber sensors functionalities.[21]

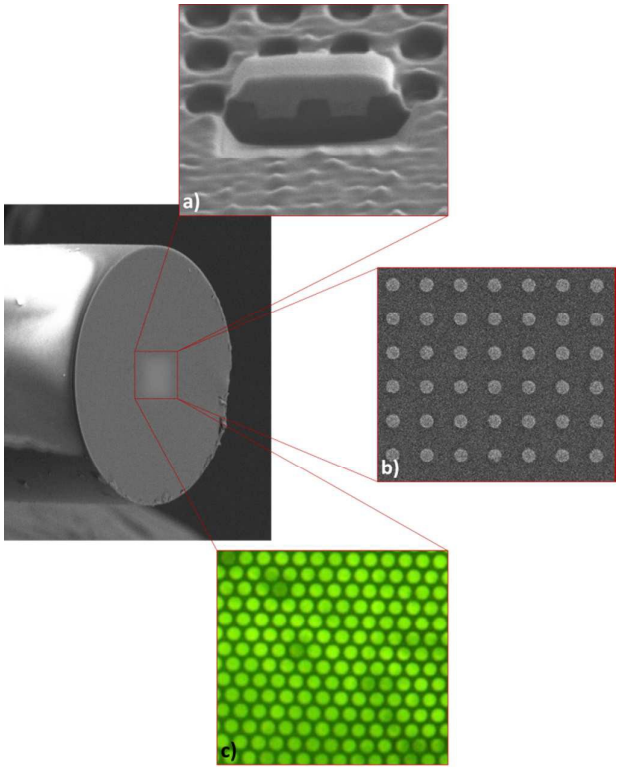

Fig. 1 SEM images of nanopatterning realized onto optical fiber tip via top-down approach (a, b) and a fluorescence microscopy image of a nanostructure obtained through the bottom up approach (c).

In the particular context of (bio)chemical sensing applications, the labs design typically involves the exploitation of advanced photonic systems providing light control at nanoscale, which are combined with sophisticated chemistry, with the ultimate goal of enhancing the light matter interaction in specific spatial locations.

The interaction between the biological elements and the light may take place either within the fiber itself (for example inside the air tunnels of microstructured optical fibers cladding[22–26]) or on functional materials integrated on the fiber surface, i.e. around the fiber side surface (typically on lengths of millimeters) or on its tip. Lab-around-fiber devices can be, on

their turn, classified depending on the mechanism exploited for extracting photons travelling along the fiber core and guiding them towards the external cladding region, where the light-matter interaction occurs. Two main subclasses of these devices can be identified; the first one deals with optical fiber probes characterized by the partial or total reduction of the fiber cladding (Taper, D-Fiber)[27–29]. The second one relies on the use of diffraction gratings inscribed in the fiber core (Tilted Fiber Grating and Long Period Grating) able to couple light form core to cladding modes[29–31]. Lab on Fiber Technology thus embraces different platforms that are classified depending on where the sensitive element, i.e. the lab, is. In this work, we restrict our attention only on devices where the sensitive element is placed on the fiber tip (i.e. Lab-on-tip configurations).

Patterning of optical fiber tip has a long history, and first examples of simple modifications (mainly "decoration" or "self-assembly") for SERS applications date back to the 90s refs.[32] Since then, many prestigious research groups in the photonic community have focused their efforts to address the major challenges to fuse the micro- and nano-technology world with optical fibers.

These efforts are mainly devoted to adapt well established nanofabrication strategies to work with an "unconventional" substrate such as the optical fiber tip. Recently, these strategies have been discussed in an exhaustive review[20]; here, we give only a short resume of the main methods used to generate the so called Lab-on-tip devices. To the scope, both top-down and bottom-up fabrication approaches have been reported; examples of nanostructures realized onto the fiber tip are shown in Fig. 1.

The top-down approach relies on standard microfabrication technologies, including electron-beam lithography (EBL)[14,18,20,33–36] focused ion-beam (FIB) milling[37–39], reactive ion etching (RIE)[33,40] and hybrid techniques, which transfer nanostructures realized on planar substrates to the fiber tip.[40–45] An example of the hybrid techniques was reported by Lipomi *et al.*, that use an ultra-microtome equipped with a diamond knife to manually transfer an arrays of gold nanostructures embedded in thin epoxy slabs to the fiber tip.[44] Following the transferring approach, a monolithic silicon photonic crystal fiber-tip sensor was realized employing a combination of EBL and RIE for the structure fabrication and FIB milling for the transferring step.[40] A method based on a UV nanoimprint and transfer lithography technique was also introduced for the fabrication of optical probes for photonic integrated circuits based on a waveguide-to-fiber gold grating coupler.[44] Although these methods rely on well-assessed fabrication processes on planar substrates, the final transferring step, never trivial, plays a fundamental role in determining both the fabrication yield and the performance of the final device.[41,43] To overcome this drawback, alternative approaches based on direct-write patterning of the fiber tip have been explored. The key aspect of these methodologies is to adapt all the standard fabrication processes and tools in terms of material deposition, subwavelength patterning and lift-off process, to operate directly on the optical fiber tip.

In 2006, Iannuzzi *et al.* fabricated, via FIB system, a high-sensitivity microcantilever- on the fiber tip.[46] By microstructuring the fiber end surfaces, Liberale *et al.* demonstrated a miniaturized fiber based optical tweezer.[47] FIB has been also used to efficiently mill on the end facet of a photonic crystal fiber (PCF) a microchannel enabling the selective fluid filling into a desired pattern of PCF air holes.[48] Moreover, both circular and bow tie-shaped nanoholes arrays were fabricated on gold films deposited on the tips of optical fibers.[49-50] Similarly, Dhawan *et al.* reported the fabrication of nanopillars and nanoholes in optically thick metallic films.[37] Another type of procedure, based on spin coating process and EBL patterning has been used by Consales *et al*. The authors realized an optical fiber probe based on 2D hybrid metallo-dielectric nanostructure, whereby an array of nanoholes in resist was metallized.[14] Moreover, by using EBL, and RIE or lift-off process, ordered arrays of gold pillar have been fabricated on the fiber.[33,36,51] The lift-off[36,51] or RIE[33] processes were used to remove the sacrificial e-beam resist in order to obtain the desired gold pillar design onto the fiber tips. Although, the direct top-down methodology allows to produce resolute and repeatable patterns, it remains an expensive approach. A possible alternative, is the bottom-up methodology, based on self-assembly procedures. Unfortunately, these processes, are difficult to implement on confined substrates. Attempts mostly based on metallic nanoparticle self-assembly have been reported so far.[52–53] All of these studies reveal that, although the self-assembly approach provides a high production throughput without using high-cost microfabrication facilities, synthesizing metallic dielectric crystals by assembling solid objects in a highly ordered fashion directly on a fiber tip still remains a major challenge.

Even though most of the illustrated approaches need to be further optimized before making lab-on-fiber devices ready for commercial use, their potentialities and effectiveness have been clearly demonstrated. This has led to the development of many prototypes of Lab-on-Fiber devices useful for chemical and biological sensing, that are reviewed in this work.

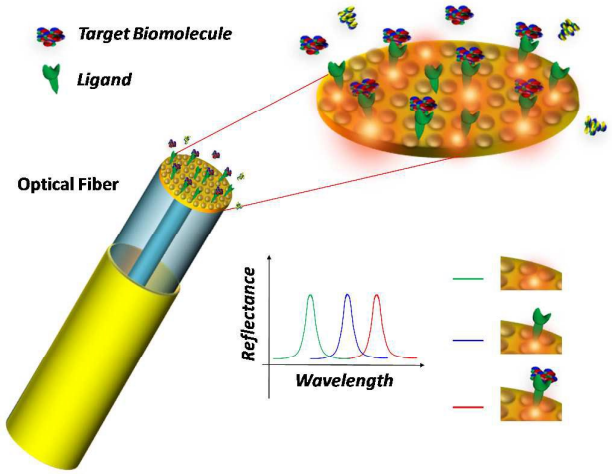

Fig. 2 Schematic of the Lab-On-Fiber biosensing principle. A metallic nanostructure supporting a resonant plasmonic mode is integrated on the optical fiber tip. When a molecular binding event occurs at the sensor surface, the reflectance peak associated to the plasmonic mode shifts towards longer wavelengths.

In the majority of cases, the light-matter interaction on the biosensor surface is achieved through the integration of thin layers of nanoparticles or nanostructures supporting resonant modes, highly sensitive to local modifications of the surrounding environment (as schematically represented in Fig. 2). In fact, because of the binding of an analyte molecules layer, the refractive index changes are restricted only to local modifications occurring at the fiber sensor surface. The materials used can range from plasmonic[54] to PCs[55], which precisely locate highly concentrated optical fields and facilitate the interaction of these fields with local chemical variations. Specifically, metallic nanostructures support both propagating and localized surface plasmon resonances (LSPRs) which exhibit high local electromagnetic field intensity confined around the boundary of the metal structures of sub-wavelength dimensions. SPRs could be exploited also for surface enhanced Raman spectroscopy (SERS) which involves the study of molecules adsorbed to the sensor surface.[56] Moreover, the light-matter interaction enhancement can be also achieved by exploiting both dielectric and semiconductor supporting photonic resonant modes (i.e. guided resonances and cavity modes) that do not suffer from the intrinsically lossy character of plasmonic resonances.

According to the materials used and the physical principle that is exploited, we have divided the rest of this review dedicated to lab on fiber tip biological sensors in two main sections, related to (i) plasmonic and (ii) photonic probes. The first section is divided in two subsection regarding both LSPR and SERS based optical fiber platforms.

Plasmonic optical fiber probes

Metallic structures may be designed to support, at specific wavelengths, SPRs i.e. surface waves (charge density oscillations) occurring at the interface of two media with dielectric constants of opposite signs, such as a metal and a dielectric. The electric field distribution associated with SPRs is enhanced at the surface and decay exponentially into the media on either side of the interface. Typical decay lengths of the electromagnetic field observed in surface plasmon are in the order of 100 nm. Every modification at the sensor surface results in a shift of the resonant wavelengths that, on its turn, translates to a reflected intensity signal change. The first SPR bio-chemical sensor was demonstrated in 1983 by Liedberg *et al*.[57] Since then it has been extensively explored and has gradually become a standard label-free tool to study the interactions between the target and bio-recognition molecules. Indeed, many commercial instruments provided by tens of companies worldwide, exploit SPR phenomenon to monitor the thermodynamics and kinetics of biological binding processes. The principle, development, and applications of SPR biosensors have been well described in several excellent review papers.[58–61]

In addition to the SPRs, metallic geometries such as nanoparticles or nanoholes can also involve the excitation of LSPRs. Different from SPR, LSPRs are non-propagating modes and are characterized by resonant wavelengths depending on the size and the shape of the objects and the dielectric constant of both constituent and environment materials, being well suited for detecting local environment changes. Since in LSPR the induced plasmons oscillate locally to the nanostructure rather than along the metal-dielectric interface (as in the case of Surface Plasmon Polaritons, SPPs), the exponential decay length of the electromagnetic field observed in LSPRs is in the order of 10 nm. This property has an impact on biosensing applications. In fact the shorter field decay length for LSPR reduces the sensitivity to interference from solution refractive index fluctuations whilst providing increased surface sensitivity to refractive index changes on the surface.

LSPRs play an important role also for enhancing Raman scattering based sensing. Raman scattering (RS) is an inelastic scattering process occurring when monochromatic light (usually from a laser) interacts with a molecule; the scattered laser photons are shifted in frequency by the energy of the molecule characteristic molecular vibrations. The energy difference between the incident photon and the scattered photon gives information about the vibrational modes in the molecules. Since each molecule has its own set of vibrational modes, Raman scattering can be considered as the fingerprint of a molecule. This technique has the advantage of molecular specificity over most of other spectroscopic techniques such as fluorescence spectroscopy.[62]

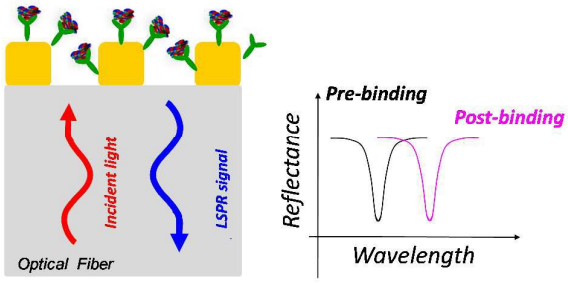

Fig. 3 Operating principle schematic of the LSPR-based optical fiber probe. A red shift of LSPR peak is observed in the reflection spectrum when the analyte interacts with the ligand on the surface of a metal nanostructure.

The main drawback of RS is that the Raman signal is usually very weak because of the small cross-section (typically 10^{-30}-10^{-25} cm^2 per molecule) resulting in a difficult detection of the analyte at low concentrations. In order to improve the sensitivity, the so called SERS technique is exploited, in which the molecule is adsorbed close to a metallic nanostructure surface supporting LSPRs with strong electromagnetic field enhancement.[63–64] Typically, for roughened metal films, the enhancement factor (EF) is around 10^3 – 10^5 while for nanoparticles aggregates, stronger enhancements of 10^7 – 10^9 can be achieved.[65] The electric field enhancement in the gap between nanoparticles, results in "hot spots" of stronger Raman signal enhancement.[66]

The following two subsections are dedicated to both LSPR and SERS based optical fiber probes.

LSPR-based probes

LSPR based Lab-on-tip biosensors have been here classified according to the approach adopted for their fabrication.

With a direct approach Consales *et al*. realized an optical fiber probe based on 2D hybrid metallo-dielectric nanostructure, whereby an array of holes in resist was metallized to produce a LSPR.[14] The authors have investigated the surface sensitivity of the proposed devices, which in turn can be considered the key parameter when dealing with chemical and biological applications. Experimental results have revealed the capability to detect nanosized overlays deposited on the sensor substrate, demonstrating the effectiveness of the proposed platform to be used as high sensitivity label free biosensor. They have analyzed the effect of the metallo-dielectric crystal size on the spectral features exhibited by the integrated platform demonstrating that the sensitive area (i.e., the patterned area on the fiber tip) can be reduced down to only 20 × 20 μm^2 without affecting the sensor operability.[35] Pisco *et al.* demonstrated a fabrication process based on self-assembly technique which offer a high production throughput without using sophisticated and expensive technologies.[67] By exploiting the so called breath figures methodology, regular and ordered metallo-dielectric crystals have been successfully integrated onto the optical fiber tip, supporting interferometric effects assisted by surface plasmon excitation at the metallo-dielectric interface. The realized device has been tested for chemical sensing application by simply dipping the probe in liquid solution with different refractive index and an exceptional refractive index sensitivity of ~2300nm/RIU has been found.

The two above mentioned works represent a valuable prospective to obtain label-free bio-chemical sensor; in the following we present some works where lab on tip devices have been effectively tested and validated as bio-chemical sensing platforms.

Lin *et al*. report on an LSPR biochemical sensing based on an ordered array of gold nanodots fabricated on the optical fiber end facet using EBL and Reactive Ion etching.[33] This sensor shows an high sensitivity (195.72 nm/RIU) for detecting changes in the bulk refractive indices, as well as label-free affinity sensing of bio-molecules using biotin/streptavidin as receptor/analyte.

The same group has successively demonstrated a miniaturized LSPR coupled fiber-optic nanoprobe capable of label-free, sensitive detection of a cancer protein biomarker, the free prostate specific antigen (f-PSA).[36] The biosensor is based on a gold nano-disk array that is directly fabricated at the fiber facet by using EBL and metal lift-off process. The probe has been functionalized via a self-assembled monolayer (SAM) of alkanethiolates on the gold nanodisk array to attach a capture ligand, an anti-PSA antibody,as a selective immunoassay. The sensor exhibits the lowest limit of detection (LOD) at 100 fg/mL (3 fM) of f-PSA in phosphate buffered saline (PBS) solution.

With a similar approach, Ricciardi *et al*. have recently reported on an optical fiber biosensor capable to detect human Thyroglobulin (h-Thyr) at nanomolar concentrations.[51] The device is essentially based on a metallic nanostructure, directly fabricated on the fiber tip by means of EBL and lift-off process, supporting LSPRs in the NIR (Fig. 4a and 4b). The fiber tip has been chemically functionalized with a mixed SAM of thiols (mixtures of 16-mercapto-1-hexadecanoic acid and 11-mercapto-1-undecanol) allowing the covalent immobilization of anti-Thyroglobulin monoclonal antibody (MA5-12048), after proper activation of the surface carboxyls with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and N-hydroxysuccinimide (NHS).

Fig. 4d shows the measured resonance wavelengths corresponding to the reflectivity maximum as a function of time, when the optical probe is immersed in the Thyroglobulin solutions at 0.4 µg/mL and 4 µg/mL in PBS (i.e. the sensorgram). As expected, the peak red-shift increases with increasing Thyroglobulin concentration. Specifically, wavelength shifts of 0.92 nm and 2.82 nm (estimated as a difference between two successive immersions in the same buffer solutions) for concentrations of 0.4 µg/mL and 4 µg/mL, respectively, have been measured. It is important to remark that after detecting different h-Thyr amounts, the baseline is fully restored by treatment with NaOH solution. Under these conditions the peak wavelength returns to its initial value following a wash in the running buffer.

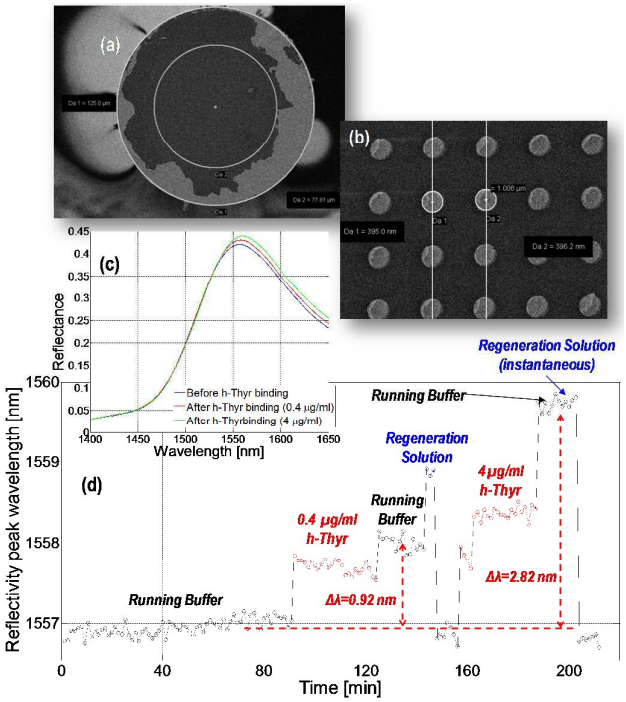

Fig. 4 (a) SEM image (top view) of the optical fiber probe; (b) zoomed-in image of (a); (c) Experimental reflection spectrum of the fabricated device before and after the h-Thyr binding (0.4 µg/mL and 4 µg/mL) in PBS; (d) Sensorgram obtained for the detection of 0.4 µg/mL and 4 µg/mL of h-Thyr. The baseline regeneration step is also shown.

Following a different approach, Jia *et al*. have implemented a plasmonic optical fiber probe by transferring periodic Au nanostructures from patterned templates onto end-faces of multimode optical fibers using an epoxy adhesive.[68] They design a special plasmonic fiber that simultaneously implements multimode refractive index sensing (transmission and reflection) with remarkably narrow linewidth (6.6 nm) and high figure of merit, which are both among the best reported values for SPR sensors. They further demonstrate a real-time

immunoassay (between Bovine Serum Albumine (BSA) and anti-BSA), relying on their plasmonic fiber integrated with a special flow cell. A PBS buffer is first injected into the flow cell to define the baseline of resonant wavelength. Successively a 50 mg/mL BSA solution in PBS buffer flows over the gold nanostructures on the fiber tip. After a PBS washing step, a 4.3 mg/mL anti-BSA solution is injected in the flow cell. After washing out the unbound anti-BSA molecules by PBS rinse, the resonant wavelength shift (530 pm) is definitely measured. The LOD of the realized biosensor is 8.5 pg mm^{-2}.

Differently, following the bottom-up approach, Jeong *et al*. fabricated a fiber optic-LSPR biosensor using spherical gold nanoparticles (AuNP) on a flattened end-face of a multimode optical fiber.[52] The AuNPs were synthesized by the Turkevich method and were immobilized on the end-face of the optical fiber by using a SAM. The fabricated fiber optic LSPR sensor was used for the detection of the antibody–antigen reaction of interferon-gamma (IFN-g) and PSA with LOD of approximately 2 and 1 pg/mL respectively. Specifically hydroxyl functional groups were formed on the end-face of the optical fiber by dipping it in a piranha solution, while amino functional groups were formed on the hydroxyl functional groups by immersing the sensor in an APMES solution (5% (v/v) 3-aminopropyldimetylethoxysilane). Au NPs were immobilized on the SAM by immersing the sensor in a gold colloid solution. Finally the antibodies (antibody IFN-g and antibody PSA) are adsorbed on the spherical Au NPs because the Au NPs have negative charges on their surface. Successively the sensor surface is treated with BSA to suppress the nonspecific binding. BSA is adsorbed on the whole surface of the fiber sensor in order to suppress the binding of the antigen with the surface of the sensor except for the area covered by the antibody.

On the same approach, Sciacca and Monro report on a LSPR dip biosensor based on anchoring metallic nanoparticles (gold and silver) to the tip of a cleaved optical fiber.[53] The optical fiber tip was functionalized with a solution of polyallylamine hydrochloride (PAH). PAH is a positively charged polyelectrolyte adsorbing onto the negatively charged glass surface, and introducing amine groups to electrostratically link the metallic nanoparticles. The PAH-terminated fiber was immersed into the Au NP solution and then placed in a 10 µM biotin-thiol single-strand DNA (ssDNA) solution to promote covalent binding between the thiol-terminated ssDNA and the Au NP. The biotin terminated Au NP were exposed to 400 nM Neutravidin, which binds specifically biotin, forming a strong noncovalent bond. After that, the sample was further functionalized with a solution of biotinylated antiapolipoprotein E (apoE) IgG (330 nM, MabTech) allowing the biotin function of antibodies to bind to free groups on Neutravidin, resulting in Au NP terminated with anti-apoE antibodies. Silver nanoparticles (SNP) were then linked to the fiber and functionalized by using the same functionalization process followed as for Au NP.

The developed biosensor is proven to be effective in detecting two different gastric cancer biomarkers (apolipaprotein E and CLUsterin) in clinically relevant conditions simultaneously with a limited cross-reactivity and in a short time frame. Moreover the authors have demonstrated that smaller quantities of nanoparticles lead to greater sensitivity.

SERS-based Probes

There have been several applications of optical fibers in Raman spectroscopy, but only a few of them really exploit SERS for constructing compact optical sensors. There are a number of SERS probes that collect signal through a fiber, but they are illuminated externally.

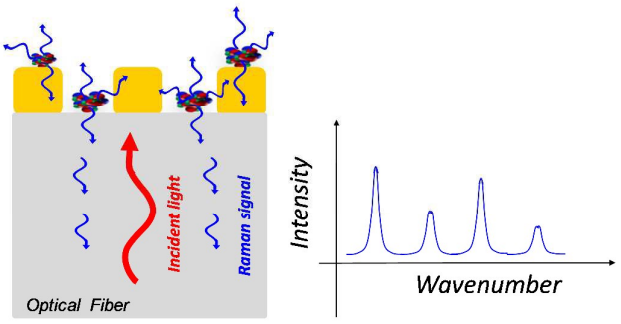

Fig. 5 Operating principle schematic of the SERS-based optical fiber probe. LSPR excitation supported by the metallic nanostructure transfers energy to the target molecule immobilized on the surface, allowing the enhancing of the Raman signal and vibrational modes to be detected.

For instance, one of the first fiber optic SERS sensors consisted of one fiber carrying the laser light onto a separate SERS-active substrate and a second fiber collecting the scattered light from the substrate.[69] Another approach was to produce a SERS-active surface directly on the end of the excitation fiber by depositing thermally evaporated silver on an abrasively roughened fiber tip.[32] SERS surfaces have been also fabricated (on optical fiber tips) by means of a femtosecond laser scanning etching process, successively coated with a thin layer of silver through thermal evaporation.[70] In this case, a high quality SERS signal was detected by using a Rhodamine 6G (R6G) solution with an approximate concentration of 10^{-7} M. On the same line of argument, the fabrication in batch of silver nanorod (AgNR) arrays deposited onto the distal end of an optical fiber by oblique angle deposition has been proposed.[71] The AgNR coating allows maximum light transmission so that the probes have been used, with a relative compact forward scattering optical configuration, to detect both trans-Bis(4-pyridyl)ethane (BPE) in MeOH and adenine-1/2H_2SO_4 in Tris–hydrochloridewith a LOD of 10^{-7} M.

However, the above mentioned configurations are based on unidirectional light propagation. As a matter of fact the optical fiber is only used to couple Raman signals (excited with external illumination in front of the fiber tip) to spectrometers (located at the opposite end) or to effectively illuminate the SERS surface with Raman signals collected by the spectrometers located in front of the probe facet.

In many situations (especially for in-situ detection), the same optical fiber has to be used to both deliver the irradiating light and collect the resulting SERS signal in a remote end detection mode. This capability is made possible by bidirectional propagation of the excitation light. Such a configuration would

be given in a so-called optrode design, a fibers bundle or a single fiber carrying both excitation radiation and Raman signal. The tip of the fiber itself should be modified to form a SERS-active surface which scatters the enhanced signal from analytes in its surroundings back into the fiber. With a fiber SERS probe in the optrode configuration it is possible to perform measurements in situ for multiple analytes detection by dipping the probe in the solution containing the target analyte molecules and measuring the reflected spectra.

Between the late 90s and early 2000s the first bidirectional probes have been implemented. These probes consisted of a fiber with a modified fiber facet that is roughened[72–73] or covered with an array of self-assembled colloids[74] and successively coated with a thin layer of metal. Thereafter different approaches and methods have been proposed in order to produce SERS based fiber optic probes for remote chemical and biological sensing and detection applications.

A photo-induced growth and deposition process has been applied to immobilize SNPs on the end of an optical fiber tip.[75] Basically the fiber was immersed in a growth solution (prepared by mixing 1.0 mM $AgNO_3$(aq) and 1.0 mM aqueous trisodium citrate in a molar ratio of 1:1) and the laser beam was introduced into the fiber core. The deposited SNPs are widely aggregated in that a large number of hot spots are produced in order to obtain a sizable enhancement of the Raman intensity of probing molecules. The SERS activity has been quantified by a probing molecule i.e. BPENB(1,4-bis[2-(4-pyridyl)-ethenyl]-benzene) at different concentrations. Clearly the SERS signal increases as the concentration of BPENB increases and the LOD was found to be 1.0 nM. For doing so, the fiber tip was directly immersed in the BPENB solution and the SERS spectrum was extracted by a Raman spectrometer optically connected to the distal end of the fiber tip.

Shi *et al*. proposed a double substrate sandwich structure based on tip coated multimode fibers.[76] The fiber is coated with SNPs to obtain the SERS surface. Upon dipping the coated fiber probe into the solution containing a mix of SNPs and target analyte molecules, the randomly formed SNPs structures sandwich the analyte molecules in between. The improvement of SERS sensitivity is attributed to the extremely large electromagnetic enhancement between SNPs placed in the sandwich configuration. This probe was tested using R6G molecules and the sensitivity has been found to be about ten times better than that using a single SNP substrate in solution, with a LOD of 10 nM.

The same group has successively proposed a similar approach for label-free detection of the proteins lysozyme and cytochrome c by using a tip-coated multimode fiber with a double-substrate structure.[77] In this latter case, the sandwich nanostructure is formed by the cetyltrimethylammonium bromide (CTAB)-capped positively charged SNPs coated on the fiber tip and the negatively charged SNPs in the bulk solution where the protein samples are diluted. The electrostatic force from the oppositely charged surface decreases the gap distance between these two types of SNPs, therefore facilitating the formation the “sandwich” structure. Since the electro-magnetic field between the SNPs increases when the gap distance decreases, the shorter gap distance can lead to a stronger “hot spots” and, therefore, an increased SERS signal. A detection limit for both proteins of 0.2 µg/mL has been found.

Although it can be realized with low cost and rapid fabrication technique, an arbitrary pattern of metallic nanoparticles, however, is generally not the optimal sample configuration for maximizing the SERS signal measured in a detector, since the strength and directionality of enhanced electric fields radiated by a particle are highly dependent on the size and shape of the nanoparticle. Non optimal coupling of light to nanoparticles can result in the excitation of lossy, non-radiative surface plasmon modes as well as inefficient scattering of the SERS signal. Lithographic techniques, instead, enable the definition of SERS substrates with nanostructures of specific shapes and spacing.

Based on these consideration, Kostovsky *et al*. developed a simple, low cost technique for self-aligning nano-imprinting (with feature separations smaller than 15 nm) arrays of optical-fiber facets with 2D polymer nanostructures.[78] In particular they have demonstrated a capacity for 40 optical fibers imprinted with the cicada pattern, and for the 10 fibers imprinted with the self-assembled nanostructure of anodized aluminum oxide pattern. Imprinted facets were metallized with 60 nm Ag by thermal evaporation at normal incidence, under rotation. The probes were then immersed in a test analyte solution of 10 mM thiophenol in ethanol, allowing the thiophenol to adsorb on the Ag surface. Excess thiophenol was rinsed away with ethanol, and the fibers were air dried prior to SERS testing. The bi-directional functionality was then tested by taking two SERS measurements, first by direct interrogation of the nanostructured facet, then in the through-fiber optrode configuration, where the fiber core carries both the excitation and scattered light. Distinct thiophenol peaks are present in all fiber measurements, and through-fiber spectra show reasonable signal-to-noise ratio, despite additional losses associated with the optrode geometry.

The application of standard lithographic techniques on the optical fiber tip provides a method for producing perfectly ordered metallic nanostructures with well-defined geometry, which allows the optical response of the probe to be tuned and the density of “hot spots” generating the enhanced Raman signal to be controlled. E.J. Smythe *et al*. demonstrated a bidirectional fiber optic probe whose facet is integrated with an array of gold optical antennas designed to enhance Raman signals.[79] The array of nano-antennas was first defined by EBL on a silicon wafer and subsequently stripped from the wafer and then transferred to fiber tip. Simultaneous detection of benzenethiol and 2-[(E)-2-pyridin-4-ylethenyl]pyridine was demonstrated through a 35 cm long fiber. SERS measurements were carried out by immersing the end of the fiber, containing the metallic features, in a 3 mM benzenethiol solution in methanol for 12 h. The modified facet of the fiber was then rinsed in methanol for removing any benzenethiol molecules not absorbed to the gold antennas. Moreover the ability to control the size and spacing of the antennas enables the EF of the transferred array to be estimated. EF values estimated after focusing a laser directly onto the transferred array are of about $2\text{-}5 \times 10^5$.

By exploiting a direct writing approach based on FIB milling of a gold layer deposited on the single mode fiber tip, Andrade *et al.* fabricated both circular and bow tie-shaped gold nanoholes arrays.[80] The resulting optical fiber probes were used for SERS measurements in both back- and forward-scattering configurations, yielding promising performance in both detection arrangements. It was demonstrated that the SERS

intensity is dependent on the size and shape of the nanoholes, on the periodicity of the arrays and on the thickness of the gold film. The bow tie nanostructures, although polarization dependent, presented a better performance than the circular holes arrays, due to the strongest field enhancement at the tips of the structures.

Another approach based on interference lithography was proposed by X. Yang and coworkers which proposed a fiber probe based on silver coated rectangular array (with a pitch of 317 nm) of nanopillars providing a very high density of SERS "hotspots".[81] The typical fiber length was around 10 cm. For the optical characterization of the fiber SERS probe, reflectance spectra were measured in both the front end and the remote end configurations by using a white light source. SERS performance has been tested with trans-1,2-bis(4-pyridyl)-ethylene monolayer and an EF of ~1×10^7 has been achieved by focusing the laser (at 514 nm) directly onto the nanopillar array (for the optrode configuration, the SERS sensitivity is about 1/5 of that obtained in the front end configuration). The protein samples were diluted 1/10 with the aggregation agent (0.1 M Na_2SO_4, pH = 3) and then were mixed with the citrate-reduced SNPs (1:5, v/v). SERS measurements were simply performed by dipping one cleaved end into CTAB-capped SNP solution. They also demonstrate that this probe can be used for in situ remote sensing of toluene vapor at room temperature by the remote end detection.

Overall in all the device presented so far and used for the remote sensing application, there is a tradeoff between minimizing the metal absorption loss and maximizing the SERS enhancement. Therefore, how to decrease coupling losses and improve SERS signal intensities would be one of the focuses of the future work for optical fiber based probes working in the optrode configuration.

Photonic optical fiber Probes

The configurations discussed so far are based on the integration on the fiber tip of metallic structures, in the form of both nanoparticles and patterned layers. In all these cases the light matter interaction was essentially assisted by the strong electromagnetic field enhancement due to the excitation of plasmonic resonances. In this latter section we focus the attention on other lab-on-fiber based platforms involving the integration on the fiber tip of pure dielectric/semiconductor nanostructures able to efficiently manipulate the light flow and trap light on sub-wavelength scales. Although none of these configurations has been already tested in a real scenario of biological application, lab on fiber tip devices based on dielectric/semiconductor nanostructures have been shown to be very promising platforms for label free biosensing. The low loss character of most dielectric or semiconductor materials at VIS-NIR wavelengths makes it possible to achieve resonant effect with high Q factors that could in principle enhance the sensor sensitivity.

Photonic Crystal slabs (PCSs) consisting of one- or two-dimensional periodically patterned dielectric layers (typically with a thickness of a few hundreds of nanometers) have elicited a great attention in the lab on fiber technology community. In fact, in a PCS, light can be confined to in-plane guided modes by the high refractive index contrast between the dielectric material and the external medium (with consequent no coupling to externally incident optical beams) or can be confined to the so called "guided resonance" (GR) modes in the slab, for which coupling to externally incident optical beams is allowed.[82–83] The resonance effect arises when the orders diffracted by a normally incident wave are coupled to the leaky waveguide modes (i.e. the GRs) supported by the slab.

When PCS are assembled on the fiber tip, light can be thus coupled back and forth between the dielectric structures and the optical fibers for efficient optical readout that avoids a bulky free-space setup, as in the case of photonic lab on chip devices. The possibility to excite electromagnetic waves strongly confined within the slab and yet capable of coupling to the external radiation, provides an effective and appealing way to sense the external environment. By appropriately designing the physical and geometrical parameters of the PCS, it is also possible to set the number and the electric field distribution of the modes involved in the coupling process.[84]

Some studies have demonstrated that sensitivity associated to photonic modes may result higher than that associated to plasmonic modes.[85] Moreover, photonic modes, having most of their energy concentrated in the dielectric layer away from the metal surface affected by losses, have longer propagation lengths than SPP modes, increasing the Q factor.[86]

On these bases, I. Jung and coworkers have experimentally demonstrated a probe for refractive index sensing, based on the integration of a silicon PCSs supporting GRs.[87] The PC slab was first fabricated on standard Si wafers (using a single photolithography mask and a combination of isotropic and anisotropic etching) and then assembled onto single mode optical fiber facets (50 µm × 50 µm × 0.5 µm). The measured sensitivity for de-ionized water/isopropanol solution with different concentrations is ~213 nm/RIU with a refractive index resolution of Δn ~5×10^{-6}. GRs excited at its resonant wavelength determine the features of the reflection spectra. The interesting point is that different features of the reflectance spectra (and thus different GRs) experience different amounts of shift in response to changes in concentration. This is because each GR results in the dissimilar spectral shift across the wavelength range on the external refractive index variations.

The light localization in a PCS can be enhanced by introducing PC cavities (PCCs) that are essentially a defect created by the absence or by changing the size and spacing of one or more adjacent holes in a PC microscale optical structures.[88–89] The introduction of defects leads to the creation of resonant modes with wavelengths within the band gap which are laterally confined by the surrounding PC. The PCC can be designed in such a way to allow the out-of-plane coupling (i.e. the defect mode is not is vertically confined) thus enabling the possibility to be integrated on the optical fiber tip. This approach results in the excitation of PCCs modes with very high Q-factors and modal volumes in the order of a cubic wavelength.

G. Shambat and coworkers developed a method to integrate semiconductor (both silicon and GaAs) PCCs (with quality factor of 2-4 × 10^3) onto optical fiber tips by using an epoxy transfer process.[90] In order to achieve a large mode area coupling, coupled cavity arrays have been exploited. Before the transferring step, the PCCs were fabricated through standard EBL, dry etching, and undercutting of GaAs layer with embedded high density InAs quantum dots emitting at 1300 nm as internal light sources. The PCC optical fiber tip probe

can operate as an effective nanoparticle sensor for both gold and iron oxide and can even quantitatively determine nanoparticle concentration.[91] In addition to PC, resonant effects in photonic circuits can be effectively achieved with optical ring resonators (RRs).[92] A RR basically consists of an optical waveguide which is looped back on itself, such that a resonance occurs when the optical path length of the resonator is exactly a whole number of wavelengths. RR thus supports circulating waveguide modes with resonant wavelengths that are related to the effective optical path length of light inside the ring; when the refractive index near the RR surface is modified (for example due to the capture of target molecules on the surface), the path length will change which in turn leads to a shift in the resonance wavelength.

Based on this concept, C. Lerma Arce *et al.*, have proposed an optical fiber probe sensor based on silicon on insulator (SOI) RRs that could be useful for label-free biosensing.[93] The out of plane to in plane coupling is made possible thanks to a grating coupler placed in correspondence of the optical fiber core. As a proof-of-principle to show the capabilities of the fiber probe, the sensitivity for refractive index changes of aqueous solutions was measured. The achieved sensitivity of 70 nm/RIU was in line with the one measured for a similar SOIRR sensor not integrated on the fiber facet meaning that the proposed fabrication process had no detrimental effect on the device performances.

Conclusions and outlook

In conclusion, Lab on Fiber can be now considered more than a simple vision. In not too distant future, it could represent a disruptive key enabling technology providing new ways for the implementation of "all in fiber" autonomous multifunction sensing platform able to analyze sensorial data, providing radically new diagnostics properties. Lab-on-fiber technology is essentially based on the addition of new features and functionalities on optical fibers involving the exploitation of those physical phenomena that are at the forefront of photonics scientific research. In fact, the light-matter interaction on the fiber surface is achieved through the integration of nanostructures supporting resonant modes, highly sensitive to local modifications of the surrounding environment such as molecular binding events. The integration of functional and multiresponsive materials at sub wavelength scale onto the optical fiber tip provides the opportunity to perform remote label-free biological sensing in a novel and exciting fashion. The development of advanced Lab-on-fiber probes requires the identification and implementation of reliable and effective fabrication techniques able to integrate functional materials defined at micro and nano-scale onto optical fiber. This obviously implies the creation of a sophisticated technological environment where microfabrication strategies and tools are specialized for working onto unconventional substrate such as the optical fiber.

Even though most of the proposed approaches need to be further optimized, first evidences of Lab-on-Tip devices for chemical and biological sensing, either based on SERS or LSPRs effects, have been successfully demonstrated. All the works carried out so far and reviewed in this paper, doubtless reveal the enormous but still not yet fully exploited potentiality of Lab-on-Fiber technology. At this stage it seems that the main limitation to definitive establishment of such a technology is still represented by the lack of stable, effective and reproducible fabrication procedures, even parallelized for mass production.

Once the fabrication issues are definitively addressed, the Lab-on-Fiber technology may finally support and eventually compete with the well-established photonic "Lab-on-Chip" technology, providing significant improvements ranging from the easiest integration of complex lighting and interrogation/detection. Nevertheless, the small cross-section and large aspect ratio of the fiber make it uniquely suited to remote, in vivo and in situ applications, by taking advantages from easy integration with medical catheters and medical needles.

It is therefore not so unreasonable to envision, for the next future, the development of smart needle-based devices with unprecedented functionalities, integration and miniaturization levels, able to monitor clinically relevant parameters in real-time, directly inside the human body. This new fascinating technological world, which in turn could be named "Lab-in-a-needle Technology", could find a direct, disruptive impact in all those cancer care applications that would strongly benefit of localized treatments. Advanced and multifunctional light-based fiber platforms, completely integrated into hypodermic needles, could be able to monitor the disease appearing, progression/regression, by quantifying cancer biomarkers concentrations in the close proximity to the tumor itself.

As a consequence, it can be safely predicted that the "Lab-in-a-Needle" technology would stimulate new research and industrial interest aimed to (i) develop radically new local biopsy tools and methodologies, and (ii) identify new classes of indicators/biomarkers, leading to a surge of activities in clinical proteomics. Lab-on-fiber devices could also be exploited to improve already commercial medical devices such as fiber optic bio-imaging probes based on optical coherence tomography, and/or active needles for loco-regional cancer treatment based on microwave, radiofrequency and laser thermo-ablation.

Although Lab-on-Fiber devices are still some years away to be ready to the market, nevertheless, there is every reason to believe that this technology will continue to more and more attract a broader interest of the scientific community in the next future, leading to the development of ever more efficient devices, and not only for biomedical applications.

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